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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,621	07/17/2003	Edna Mozes	MOZES2A	9655

1444 7590 05/14/2008

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/620,621	MOZES ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2008 and 04 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 3/04/08 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's remarks filed 1/10/08 have been entered.

2. Claims 1-15 are being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-15 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could effectively treat systemic lupus erythematosus (SLE).

As set forth previously, While the mechanism of action for the method of the instant claims is not disclosed, it appears to require inducing tolerance to self-peptides as part a treatment for an autoimmune disease. Additionally, altered peptide ligands (APLs) of self-peptides are also employed. Tolerance-inducing peptide immunotherapy is well known in the immunological arts. In some cases significant results have been demonstrated in in-bred small animal models. However, said results have not been repeated in human trials. See for example, *Marketletter* (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for multiple sclerosis, MS) and Colloral (for rheumatoid arthritis, RA) provided successful results in rodent models, however, both were complete failures in human trials. Also see Pozzilli, et al. (2000), wherein the authors demonstrate that, while the induction of tolerance for the treatment of diabetes might have been expected, it simply did not occur. The authors could only speculate as to the reasons for the trial's failure. Also note Goodnow (2001), wherein the author flatly states,

> "Obtaining the desired response [tolerance] with these strategies [tolerance induction] is unpredictable because many of these signals [tolerogenic] have both tolerogenic and immunogenic roles,"

(see the Abstract). The author goes on to teach that while the induction of oral tolerance might be considered "an attractive notion", the method has failed in humans because of the lack of understanding of the mechanisms involved (page 2120, column 2).

As set forth above, the references demonstrate that even unsubstituted peptides (peptides that are not APLs) that work in *in vivo* small animal disease models cannot be expected to work in humans. Regarding the even more unpredictable APLs, Anderton (2001), teaches that,

> "This unpredictability [of APLs] led us to argue against the use of antagonist or immune deviating APL in human autoimmune disorders" (page 370).

Indeed, the reference goes on to teach that APL administration to humans can be dangerous and that in at least one case a human trial was suspended due to adverse reactions in a significant number of patients.

Other investigators have discussed additional problems in establishing human tolerance. See, for example, Dong et al. (1999),

> "Despite the fact that it has been relatively easy to induce true tolerance in small experimental animals, translating these studies into larger animals and humans has been much more difficult to achieve. Some of the hurdles that may explain this dilemma are summarized in Table 3. *Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn*", emphasis added.

A review of the instant specification shows *no* induction of tolerance and indeed, it is unclear precisely how the examples are intended to demonstrate tolerance induction. Note that the examples involve only the use of three CDR-derived peptides in *in vitro* proliferation assays. The Inventors apparently conclude that tolerance was induced given reduced proliferation. But this minimal evidence comprises an insufficient showing that the claimed method can effectively treat SLE without stimulating an immune response, or that any peptides (including APLs) or "derivatives" capable of this action even exist. A set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses no data demonstrating the induction of tolerance, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

As set forth in the FINAL action of 7/10/07, A review of the sequences of SEQ ID NOS: 1-5 reveals them to be degenerate. The sequences are degenerate even in the critical CDR regions of the peptides, thus the term APL is used. And as the source or manner of deriving the peptide sequences is curiously absent from the specification, Applicant's argument is not persuasive.

Applicant reviews Examples 7-10 and asserts that Example 7 shows the induction of tolerance.

Applicant's review is noted. Regarding Example 7, tolerance is asserted. Regardless, the tolerization of neonatal mice with immature immune systems, *before* the induction of experimental disease, bears little relevance to the treatment of established autoimmune disease in humans with mature immune systems. Examples 8-10 disclose only cell proliferation assays which again bear little relevance to the treatment of established autoimmune disease in humans with mature immune systems.

Applicant has submitted several post-filing references in support of the method of the instant claims.

It appears the all of the references employ the same peptides "based on" CDRs 1 and 3 of the mouse 5G12 antibody, i.e., SEQ ID NOS:6 and 8. Note, it is unclear what "based on" means as the sequences are either that of the antibody, or they are not. If the sequences are not that of the antibody, it is not disclosed how they were arrived at. Further, as the antibody must comprise both light and heavy chains, it is unclear even which chain the peptides are "based on". The fact that Applicant has submitted 6 references, *all* employing peptides "based on" just 2 CDRs of a single mouse antibody, appears to demonstrate that the method of the instant claims is broader than even the post-filing art could reasonably be expected to enable. While the most recently published reference, Sthoeger et al. (2003), employs an additional 2 human CDR sequences (see Table 1), said sequences are not disclosed in the instant specification, and again, the reference discloses only *in vitro* proliferation assays (as noted by Applicant in the instant Remarks at page 15).

Applicant cites an NIH press release regarding the halting of clinical trials employing APLs.

In the cited case it is clear that the APLs of the halted trial would not have risen to the level of an invention. As set forth in the release, "Despite these adverse effects, the findings confirm that the targeted peptide plays a role in the disease and provide valuable information that may help refine this type of therapy for MS as welt as other autoimmune diseases". Note the "*may help* refine…". Clearly the use of the peptides was only an idea, an idea that in this instance proved unsuccessful. The fact that the results "*may*" lead to an advancement is encouraging, but it is not an invention.

Applicant cites MPEP 2107.03(IV).

Said citation is noted. No human clinical trial data has been required. An enabling specification is, however, required.

In the submission of a specification Applicant has many choices. Applicant can either submit a thorough discussion of the claimed invention or Applicant can submit just a minimal description of the invention itself. In choosing to disclose as little as possible, Applicant does, however, face the possibility that the invention might be limited to only that which has been disclosed. In the

instant case, Applicant has chosen to provide only a minimal disclosure. Applicant has chosen not to disclose the mechanism by which the claimed method might function and Applicant has further chosen not to disclose how the specific peptides employed in the claimed method were arrived at. Just 2 of the peptides are employed in any of the examples, and then only in models insufficient to enable methods of treating ongoing disease in humans (as set forth above). Accordingly, there is no way to determine which of the peptides encompassed for use in the instant claim might function in an effective treatment of SLE, and which might not. While Applicant's post-filing references demonstrate encouraging results with the peptides of SEQ ID NOS:6 and 8, said results are not commensurate with the scope of the instant claims.

Applicant's arguments, filed 1/03/08, have been fully considered but they are not persuasive. Applicant does not understand why the method of Claims 7 and 9 is not commensurate in scope with the enablement of the previously submitted references.

The previously considered references which were referred to as "encouraging" provide insufficient enablement for the claimed method for multiple reasons. First, they are post-filing references; they provide no enablement as of the 1995 priority date. Second, the references teach only the treatment of a murine model of SLE, thus, they do not teach a method commensurate in scope with the claimed method that would encompass the treatment of human SLE. Further, considering the application of results established in a murine model to the treatment of human disease, it is noted that Applicant has submitted a press release from the Assignee stating that in 2007 a closely related peptide (Edratide: GYYWSWIRQPPGKGEEWIG) failed to provide a reduction in SLE disease activity over a 26 week trial period in humans. Like the peptides of SEQ ID NOS:6 and 8, Edratide successfully treated murine models of SLE and was expected by the assignee to successfully treat human SLE. Thus, as with other peptide treatments (as set forth above for MS, RA, and diabetes) that were successful in murine models but failures in treatments for human autoimmune diseases, once again it has been shown that results in animal models of autoimmune disease cannot be expected to translate to the successful treatment of human disease. Indeed, a more realistic expectation would be that the methods would not work in humans and the unexpected result would be if they did.

Applicant describes the peptides of SEQ ID NOS:6 and 8 derived from the CDRs of the 5G12 antibody.

It is interesting to note that even in this instance Applicant fails to actually describe the specific considerations involved in arriving at these sequences. For example, Applicant does not disclose why the CDR1-derived peptide includes one amino acid upstream of the CDR1 sequence and 14 amino acids downstream of the sequence. Neither does Applicant disclose why an F in the middle of the CDR3-derived peptide was substituted with an E. Simply asserting, minor changes are made "taking into consideration the solubility of the peptides, their stability, and certain foreseen problems in the synthesis" does not provide an enabling disclosure. And note that these incomplete disclosures are offered only now some 13+ years after the instant application's priority date.

Applicant cites two more post-filing date references.

It is unclear how these references enable the method of the instant claims. In Eilat et al. (2000) it appears that some 7 years post-filing one of the Inventors concluded that APLs of the peptide of SEQ ID NO:6 provided unpredictable results when tested for their ability to block the induction of a murine model of SLE. Regarding the Brosh et al. (2000) reference, the same Inventor again concluded (this time in the context of the peptide of SEQ ID NO:8) that the effects of APLs were, again, unpredictable in a murine model of SLE.

Thus, in total, the record shows that the Inventors had no evidence as of the 1995 priority date that the administration of the peptides of the instant claims would provide any efficacy in the treatment of any disease. After years of experimentation the Inventors established that certain of the peptides employed in the method of the instant clams had some efficacy in the treatment of a murine model of SLE. Unfortunately, after many more years of experimentation it was recently established that a closely related peptide failed to provide a reduction in SLE disease activity over a 26 week trial period in humans. Accordingly, the rejection for lack of enablement has been maintained.

5. No claim is allowed.

6. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered

in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara, Ph.D. can be reached on (571) 272-0878.

8. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

/G.R. Ewoldt/
G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600